Nanoparticles improve delivery of medicines and diagnostics

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Tiny, biodegradable particles filled with medicine may also contain answers to some of the biggest human health problems, including cancer and tuberculosis. The secret is the size of the package.

Using an innovative technique they invented, a Princeton University-led research team has created particles that can deliver medicine deep into the lungs or infiltrate cancer cells while leaving normal ones alone. Only 100 to 300 nanometers wide -- more than 100 times thinner than a human hair -- the particles can be loaded with medicines or imaging agents, like gold and magnetite, that will enhance the detection capabilities of CT scans and MRIs.

"The intersection of materials science and chemistry is allowing advances that were never before possible," said Robert Prud'homme, a Princeton chemical engineering professor and the director of a National Science Foundation-funded team of researchers at Princeton, the University of Minnesota and Iowa State University. "No one had a good route to incorporate drugs and imaging agents in nanoparticles."

Prud'homme will discuss the work April 11 in a talk titled "How Size Matters in the Retention of Nanomaterials in Tissue," to be given at the National Academy of Sciences meeting on Nanomaterials in Biology and Medicine in Washington, D.C.

The new technique, dubbed "Flash NanoPrecipitation," allows the researchers to mix drugs and materials that encapsulate them. Similar

mixing techniques previously have been used to create bulkier pharmaceutical products and have proven practical on a commercial scale. The Princeton-led team, which includes chemical engineering professors Yannis Kevrekidis and Athanassios Panagiotopoulos, is the first to apply the technology to the creation of nanoparticles, which are particles measured in billionths of meters.

The nanoparticles are too large to pass through the membrane of normal cells, but will pass through larger defects in the capillaries in rapidly growing solid tumors, Prud'homme said.

Particles in this size range also could improve the delivery of inhaled drugs because they are large enough to remain in the lungs, but too small to trigger the body's lung-clearing defense systems, he said. This trait could maximize the effectiveness of inhaled, needle-free vaccination systems. Prud'homme's research group is part of a Grand Challenges in Global Health research project led by David Edwards of Harvard University and funded by the Bill and Melinda Gates Foundation to develop nanoparticle-based aerosol vaccines for tuberculosis and diphtheria.

"Professor Prud'homme and his group have developed novel nanoparticle systems that are particularly attractive for applications in the developing world" because of their potential for use on a large scale at relatively low cost, Edwards said.

The success of NanoPrecipitation depends in large part on the fact that some molecules are hydrophobic, or water-fearing, while others are hydrophilic, or water-loving. Hydrophobic substances, such as oil, do not mix well with water. Many pharmaceutical compounds, including many current cancer treatments, are hydrophobic, making it difficult to deliver the medications through the bloodstream, given its high concentration of water.

In NanoPrecipitation, two streams of liquid are directed toward one another in a confined area. The first stream consists of an organic solvent that contains the medicines and imaging agents, as well as long-chain molecules called polymers. The polymer chain is like a necklace of pearls with half of the pearls being hydrophopic and the other half being hydrophilic. The second stream of liquid contains pure water.

When the streams collide, the hydrophobic medicines, metal imaging agents and polymers precipitate out of solution in an attempt to avoid the water molecules. The polymers immediately self-assemble onto the drug and imaging agent cluster to form a coating with the hydrophobic portion attached to the nanoparticle core and the hydrophilic portion stretching out into the water. By carefully adjusting the concentrations of the substances, as well as the mixing speed, the researchers are able to control the sizes of the nanoparticles.

The stretched hydrophilic polymer layer keeps the particles from clumping together and prevents recognition by the immune system so that the particles can circulate through the bloodstream. The hydrophobic interior of the particles ensures that they are not immediately degraded by watery environments, though water molecules will, over time, break the particles apart, dispersing the medicine.

Ideally, the particles would persist for six to 16 hours after they were administered intravenously, Prud'homme said, which would theoretically allow enough time for the potent packages to slip into the solid tumor cells they encountered throughout the body.

In the lab, this is precisely the amount of time it takes for water molecules to work their way into the centers of the nanoparticles and degrade them. The team made their particles even more resistant to early degradation by attaching hydrophobic substances, including vitamin E, to the medicines and imaging agents before incorporating them into the

particles. Further studies of the controlled release technique currently are under way.

Prud'homme's technique is essentially the opposite of previous techniques for improving drug delivery, which is to attach molecules to drugs to make them more water soluble. "Our advance is to use this technique and turn it around so the drugs stay inside our particles until we want them to leave," he said.

Beyond using size alone to target cancer cells, the team is working with Princeton mechanical and aerospace engineering professor Wole Soboyejo to create nanoparticles that have specific linking molecules on their surfaces. These particles will bond to substances that are more prevalent in cancer cells than normal ones.

Source: Princeton University